

Per-Operative Administration of Benzodiazepine in Preventing Post-Operative Nausea and Vomiting In Patients Segregated According to the APFEL Score

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ABSTRACT

Objective: To compare the incidence of post-operative nausea and vomiting in patients with and without administration of peri-operative Benzodiazepine segregated according to the APFEL scoring system

Study Design: Quasi-experimental study

Place and Duration of Study: Anesthesia Department, Combined Military Hospital, Rawalpindi Pakistan from Jan 2023 to Dec 2023.

Methodology: Patients were divided into Group B (n=140) being given per-operative Benzodiazepine along with standard anti-emetic prophylaxis and Group N (n=140) being given standard anti-emetic prophylaxis alone after excluding patients with risk factors according to the APFEL score. Primary variables studied were the incidence of nausea and vomiting in patients assessed at 1,3,6,12, and 24 hours. Secondary variable studied was mean time post-surgery to discharge.

Results: Comparison of primary variables revealed incidence of nausea/vomiting in patients between Group B and Group N at 1 hour post-operatively was 21(15%) versus 27(19.3%) patients ($p=0.341$), assessed at 3 hour post-operatively was 13(9.3%) versus 15(10.7%) patients ($p=0.690$), assessed at 6 hour post-operatively was 08(5.7%) versus 10(7.1%) patients ($p=0.626$), assessed at 12 hours was 05(3.6%) versus 06(4.3%) patients and at 24 hours was 07 (5.0%) versus 09(6.4%) patients ($p=0.609$). Mean duration of hospital stay between both Groups post-surgery till discharge was 72.18 ± 4.15 hours for Group B versus 81.92 ± 4.25 hours for Group N ($p=0.609$).

Conclusion: We conclude that low risk patients according to Apfel criteria show no significant change in the incidence of PONV with the addition of Benzodiazepine to standard anti-emetic protocol.

Keywords: APFEL, Benzodiazepine, nausea, post-operative, vomiting

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INTRODUCTION

Post-operative nausea and vomiting (PONV) is one of the most common side effects seen after administration of general anesthesia in patients.^{1,2} It is documented that nausea and vomiting is the second most common cause (post-anesthesia care unit) after pain.³ Its post-operative incidence varies from 6.7% to 73.4% in the immediate 24-48 hours after surgery in post-surgical patients.¹ With the advent of the ERAS (enhanced recovery after surgery) protocol, the post-operative recovery time has gained importance with respect to length of stay, patient comfort and early shifting and discharge.⁴ With the lessened incidence of post-operative nausea and vomiting by using a multi modal approach, patients can be effectively managed for better outcomes.⁵

The Apfel simplified risk score was proposed in 1999 and consists of four independent risk factors that

are major risk stratification factors to the development of post-operative nausea and vomiting in patients.⁶ These include female gender, non-smoker, history of PONV or motion sickness and post-operative use of opioids.⁷ The simplified scoring system has been validated by various studies and provides a swift, cost-effective simplified risk assessment to segregate prone patients and prepare them accordingly for surgery and anesthesia.⁸ Along with conventional anti-emetics used as prophylaxis for PONV, the use of Benzodiazepines has shown to have an added effect of preventing PONV in addition to its anxiolytic properties due to their cost-effectivity and benefits of anxiolysis during general anesthesia.⁹ There have been concerns regarding the incidence of delirium in the post-operative period, but studies have shown comparable recovery times post-operatively in patients given Benzodiazepines as an added adjunct for prevention of PONV.¹⁰ Various studies have been done when using Benzodiazepines with other anti-emetics, but studies have been limited when segregating low risk patients for PONV by using the

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APFEL score to conclude whether these patients require the multi-modal approach for prevention of PONV in the post-operative period by using Benzodiazepines with standard anti-emetics.

Our study aims to compare the incidence of post-operative nausea and vomiting in patients with and without administration of peri-operative Benzodiazepine segregated according to the APFEL scoring system.

METHODOLOGY

This quasi-experimental study was carried out at the Department of Anesthesia, Combined Military Hospital, Rawalpindi Pakistan from Jan to Dec 2023 after approval from the ethical review board. Minimum sample size to be taken was calculated using the WHO calculator keeping the confidence interval at 95%, power of test at 80% with the anticipated population proportion expected to have PONV with the Apfel score 0 at 10% without anti-emetic prophylaxis versus 2% with anti-emetic prophylaxis in the first 24 hours post-operatively.¹¹ Minimum sample size comparing the two population proportions came out to be 135 for one Group. A total of 320 patients were assessed for eligibility from which 40 didn't meet the exclusion criteria. 280 patients were then included in the study protocol divided into two Groups of 140 each (Figure-I).

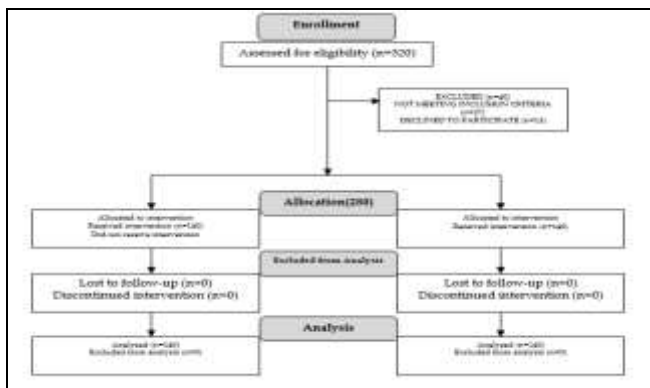


Figure-I: Phases of the Study

Inclusion Criteria: included all ASA-I and II patients between the ages of 18-55 years of age presenting for elective surgeries under general anesthesia segregated using the Apfel scoring system¹² that included male patients, smokers, no history of PONV or motion sickness and no use of post-operative opioid use.

Exclusion Criteria: included female patients, non-smokers, those with history of PONV or motion sickness, use of post-operative opioids, those with

advanced cardiac or respiratory disease, those on anti-emetics in the last two weeks before surgery, patients needing nasogastric tube insertion during or after surgery and patients unwilling to be included in the study.

The study method included all patients as per the inclusion criteria furnished. They were divided into Group B (n=140) being given per-operative Benzodiazepine along with standard anti-emetic prophylaxis and Group N (n=140) being given standard anti-emetic prophylaxis alone. All the patients included in the study protocol were first segregated using the APFEL scoring system as low risk for PONV in the pre-anesthesia clinic and were counseled regarding inclusion in the study protocol. They were then placed in one of the two study Groups using non-probability consecutive sampling via lottery method. Patients were prepped on the day of surgery in the recovery room and were administered IV Ringer lactate 1000 ml over 45 minutes. NPO (nil per oral) status was confirmed in all cases as per standard protocol. The patients were then taken to the operating room and standard monitoring was attached. Pre-oxygenation was done for 3 minutes using bag mask ventilation under spontaneous breathing or till the time end-tidal oxygen saturation was above 95% as seen on the anesthesia machine. Pre-operative medications included IV Ondansetron 4 mg stat, IV Dexamethasone 2 mg stat, IV Nalbuphine 0.15 mg/kg stat. Anesthesia was then induced with IV Propofol 1.5 mg/kg with paralysis done with IV Atracurium 0.5 mg/kg and anesthesia was maintained with inhalational Isoflurane at 1.0 MAC. Patients in Group B received IV Midazolam 2 ml (1mg/ml) stat over 30 seconds before the surgical incision while those in Group N received IV Normal saline 2 ml stat over 40 seconds as placebo. Both the preparations were marked X and Y prepared by an independent anesthetist and given to the anesthetist on duty in the respective operating rooms unaware of the study protocol. Placebo dose in Group B was done to ensure blinding.

At the end of surgery, reversal of general anesthesia was done, and patients were extubated and sent to the recovery room. They were shifted to the ward using the Aldrete standard score¹³. Patients were observed in the recovery room and the HDU after shifting for primary and secondary variables tabulated on a proforma by the resident anesthesia on duty for the next 24 hours. Primary variables studied

were the incidence of nausea and vomiting in patients assessed at 1,3,6,12, and 24 hours. Secondary variable studied was mean time post-surgery to discharge.

All statistical calculations were performed using Statistical Package for Social Sciences 26.0. Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Independent samples t-test was used to compare statistically significant means between both Groups. Chi-square test was used for frequency variables. The *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 280 patients were included in the study based on exclusion using the Apfel scoring criteria for PONV risk. They were then divided into Group B to receive IV Benzodiazepine (Midazolam) (n=140) along with standard anti-emetic protocol and Group N to receive standard IV anti-emetic protocol alone (n=140). Mean age of patients was 30.09 ± 7.50 years in Group B versus 31.04 ± 7.92 years in Group N ($p=0.308$). Mean weight was 70.72 ± 5.89 kg in Group B versus 70.88 ± 5.78 kg in Group N ($p=0.822$). Mean duration of surgery between both Groups was 80.58 ± 4.70 minutes versus 80.82 ± 4.79 minutes respectively ($p=0.669$). Type of surgery done revealed abdominal surgery was done in 69(49.3%) patients in Group B versus 70(50%) patients in Group N, thoracic surgery was done in 41(29.3%) patients in Group B versus 41(29.3%) patients in Group N, orthopedic procedures were done in 20(14.3%) patients in Group B versus 20(14.3%) patients in Group N and other procedures were done under general anesthesia in 10(7.1%) patients in Group B versus 09(6.4%) patients in Group N (Table-I).

Table-I: Descriptive Characteristics Between both Groups (n=280)

Variable	Group B (n=140)	Group N (n=140)	<i>p</i> -value
Mean Age (Years)	30.09±7.50	31.04±7.92	0.308
Mean Weight (Kg)	70.72±5.89	70.88±5.78	0.822
MEAN DURATION OF SURGERY (MINUTES)	80.58±4.70	80.82±4.79	0.669
Type of Surgery			
Abdominal	69(49.3%)	70(50%)	
Thoracic	41(29.3%)	41(29.3%)	
Orthopedics	20(14.3%)	20(14.3%)	
Other	10(7.1%)	09(6.4%)	

Comparison of primary variables revealed incidence of nausea/vomiting in patients between Group B and Group N at 1 hour post-operatively was

21(15%) versus 27(19.3%) patients ($p=0.341$), assessed at 3 hour post-operatively was 13(9.3%) versus 15(10.7%) patients ($p=0.690$), assessed at 6 hour post-operatively was 08(5.7%) versus 10(7.1%) patients ($p=0.626$), assessed at 12 hours was 05 (3.6%) versus 06(4.3%) patients and at 24 hours was 07(5.0%) versus 09(6.4%) patients ($p=0.609$). Mean duration of hospital stay between both Groups post-surgery till discharge was 72.18 ± 4.15 hours for Group B versus 81.92 ± 4.25 hours for Group N ($p=0.609$) (Table-II).

Table-II: Comparison of Primary and Secondary Variables between Both Groups (n=280)

Variables	Group B (n=140)	Group N (n=140)	<i>p</i> value
Nausea/Vomiting at 1 hour Post-Op	21(15%)	27(19.3%)	0.341
Nausea/Vomiting at 3 hour Post-Op	13(9.3%)	15(10.7%)	0.690
Nausea/Vomiting at 6 hour Post-Op	08(5.7%)	10(7.1%)	0.626
Nausea/Vomiting at 12 hour Post-Op	05(3.6%)	06(4.3%)	0.758
Nausea/Vomiting at 24 hour Post-Op	07(5.0%)	09(6.4%)	0.607
Mean Duration of Stay Post-Surgery till Discharge (hours)	72.18±4.15	71.92±4.25	0.609

DISCUSSION

The study was done in a selective Group of patients using the Apfel criteria since it includes four independent risk factors that are attributed to PONV in patients¹⁴. We aimed to find out whether using two different regimes of anti-emetic prophylaxis has any effect in patients which were low risk for PONV as their Apfel score was 0. It is pertinent to mention that even with a score of 0, the risk of developing PONV is still around 10% in 24 hours. Standard risk which increasing Apfel score of 0,1,2,3,4 is 21%, 39%, 61% and 79% respectively^{11,15}. Various studies done comparing non-segregated patients with a high risk of PONV had a significant improvement in the incidence of PONV when Benzodiazepines were added to the standard regimen for anti-emetic prophylaxis¹⁶. We aimed to find out that if those risk factors were controlled; whether we could find any significant change to recommended adding Benzodiazepines to the standard treatment prophylaxis for PONV.

Our study included patients from our pre-anesthesia clinic. Meticulous attention was paid to control risk factors for PONV given in the Apfel score. Our surgical times were also comparable between both Groups as surgical time (>60 min) has also been implicated in increasing PONV in patients. this has been proven by studies done both at the national and international level¹⁷. We tried to control these confounding factors to form an unbiased analysis in low risk patients to suggest that standard protocol for

anti-emetic prophylaxis is adequate and no added intervention is needed regardless of surgery type. We included all surgeries done at our setup for males. Female gender as a risk factor in the Apfel score prevented us from adding female exclusive surgical procedures in our study protocol.

Our study found no statistical or clinical difference in the incidence of nausea and vomiting when assessed during intervals in the immediate 24 hours post-operatively. The incidence of PONV decreased as the time passed immediately following surgery but the incidence was comparable between both Groups. This allows us to infer an important conclusion in low risk patients that standard anti-emetic treatment is sufficient and does not require any addition to the protocol. While studies have shown that when not controlling for these high risk factors, IV Midazolam is associated with a statistical and clinical significance in decreasing the incidence of PONV. With respect to the onset of delirium or confusion in patients with Benzodiazepine administration, we found that discharge times after surgeries were unaffected¹⁸. The time to recovery was slightly prolonged in the IV Midazolam Group but it was not clinically significant to warrant attention at the dose given for anti-emetic prophylaxis. This provides an important avenue to administer Benzodiazepines in patients where discharge times are usually after 24 hours. This study recommends that standard anti-emetic prophylaxis is adequate in low risk patients as per the APFEL score for surgeries under general anesthesia.

LIMITATION OF STUDY

The limitations are that the study is single center only. We did not include children and geriatric patients in our study protocol. Using Benzodiazepines after 65 years is associated with increase in the chances of delirium and this needs to be investigated further. Even with all precautions to ensure blinding and prevent bias, nature of the study may affect the results.

CONCLUSION

We conclude that low risk patients according to APFEL criteria show no significant change in the incidence of PONV with the addition of Benzodiazepine to standard anti-emetic protocol.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MAA & MEZ: Data acquisition, data analysis, critical review, approval of the final version to be published.

KA & SK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MA & MH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Administration of Benzodiazepine

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